June 7th-8th

FDA

Food Advisory Committee Meeting

Crystalline Glucosamine Sulfate

Introduction

ROTTA Pharmaceuticals Inc.

Attendants and Presenters

- **Roy D. Altman, MD**
  David Geffen School of Medicine
  University of California at Los Angeles, CA
- **Lucio C. Rovati, MD**
  Executive Medical Director
  Rotta Research Laboratorium
  Monza (MI) – Italy

Excused

- **Jean-Yves Reginster, MD PhD**
  WHO Collaborating Center for Public Health Aspect of Osteoarticular Disorders
  University of Liege – Belgium
- **Jean-Pierre Pelletier, MD**
  Notre-Dame Hospital
  University of Montreal - Canada

Attendants and Presenters

- **Martin Hahn, Esq.**
  Hogan & Hartson L.L.P.
  Washington, D.C.
- **John Barone**
  President
  Rotta Pharmaceuticals Inc
  Wall, NJ
- **Antonino Santoro, PhD**
  Head, Regulatory Affairs
  Rotta Research Laboratorium
  Monza (MI) - Italy

Active ingredient content

Crystalline Glucosamine Sulfate	1884 mg
Glucosamine Sulfate	1500 mg
Glucosamine Hydrochloride	1417 mg
Glucosamine	1178 mg

DONA ™ (Crystalline Glucosamine Sulfate) Regulatory Status

- Authorised as medicinal product in 16 countries of the EU (on 25)
- Authorised as medicinal product in several other countries in Asia, Latin America, East Europe (45 Countries in total)
- Medicinal product on prescription, reimbursed by the national health service in several countries.
- Marketed as Dietary Supplement only in USA

Crystalline Glucosamine Sulfate

- Glucosamine Sulfate is highly hygroscopic and it is not suitable for pharmaceutical preparations
- Crystalline Glucosamine Sulfate is a stabilized form of Glucosamine Sulfate
- The stabilized form of Glucosamine Sulfate contains NaCl and is in conformity to Glucosamine Sulfate Sodium Chloride described in the USP/NF 2004

Chemical formula and molecular weight of glucosamine compounds

Compound	*Chemical Formula*	*Molecular Weight*
Glucosamine	$C_6H_{13}NO_5$	179.17
Glucosamine Hydrochloride	$C_6H_{14}NO_5Cl$	215.56
Glucosamine Sulfate	$(C_6H_{14}NO_5)_2SO_4$	456.43
Crystalline Glucosamine Sulfate	$(C_6H_{14}NO_5)_2SO_4 \cdot 2NaCl$	573.31

Health Claim Petition

Dietary Supplementation of Crystalline Glucosamine Sulfate (Glucosamine Sulfate Sodium Chloride-USP/NF 2004) Reduces the Risk Of Osteoarthritis

(Joint Structure Deterioration and Related Joint Pain and Limitation of Function)

Topics

- Introduction on crystalline glucosamine sulfate (CGS)
- Clinical trial evidence of CGS in OA
- Why do the long-term therapeutic trials of CGS support the claim of disease prevention
- Effects in prophylactic animal models of OA
- Mechanism of Action
- Why "glucosamine" formulations other than CGS do not have the same body of evidence to support any claim
- Significant Scientific Agreement on the use of CGS for OA

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Crystalline Glucosamine Sulfate

Clinical Trial Evidence Supporting the Claim for Crystalline Glucosamine Sulfate (CGS)

Lucio Rovati, M.D.
Head, Dept. Of Clinical Pharmacology
Executive Medical Director
Rotta Research Laboratorium
Monza (MI) - Italy

Systematic reviews and meta-analyses of randomised controlled trials

- McAlindon et al, JAMA 2000; 283:1469-75
- Towheed et al, Cochrane Library 2001; issue 2

- Richy et al, Arch Intern Med 2003;163:1541-22

- All meta-analyses documented efficacy and safety on OA symptoms
- Rotta CGS used in 86% of trials; other glucosamine preparations gave less favourable results
- Only the third one (Richy et al) could consider the two new long-term trials of CGS.

Systematic Reviews and Meta-Analyses of RCTs

- McAlindon et al, JAMA 2000;283:1469-75
  - Placebo-controlled trials ≥4 weeks
  - 6 trials reviewed (5 with CGS)
  - Quality scores similar to standard (in OA and other indications)
  - Moderate effect size on OA symptoms, larger for longer treatments, with good safety
  - Suspect of publication bias and thus of exaggerated treatment benefit
    - (➢ Not fully supported by funnel plot analysis
    - ➢ No negative unpublished studies with CGS in the Company's archives)

Why do the long-term therapeutic trials of CGS in knee OA, support the claim of disease prevention

- Mild to moderate characteristics of the patient population
- Data on the contralateral knee
- Symptom- and Structure-Modifying effects in patients with milder characteristics at entry
- Disease outcomes in longer-term follow-up
- **Effects in prophylactic animal models, supporting a preventive role for the substance.**
- **Mechanism of action, supporting the observed short- and long-term clinical effects on symptoms and prevention of joint structure changes, by the interaction with processes that are relevant to the pathogenesis of OA.**

New Follow-Up Data from the Pavelka Trial

- **Methods**: 136 patients who had been in the trial for at least 12 months (79% of the original cohort) could be retrieved and investigated for the occurrence of total knee replacement. The median duration of follow-up with standard of care after study medication withdrawal was for further 5 years.
- **Results**:

	Placebo (N=67)	Glucosamine Sulfate (N=69)	Relative Risk (95% CI)	P
Pts. with knee replacement	11 (16.4%)	3 (4.3%)	0.27 (0.08 to 0.91)	0.021

- **Conclusions**: Treatment for up to 3 years with CGS in mild knee OA patients prevented total knee replacement during a further 5-year follow-up

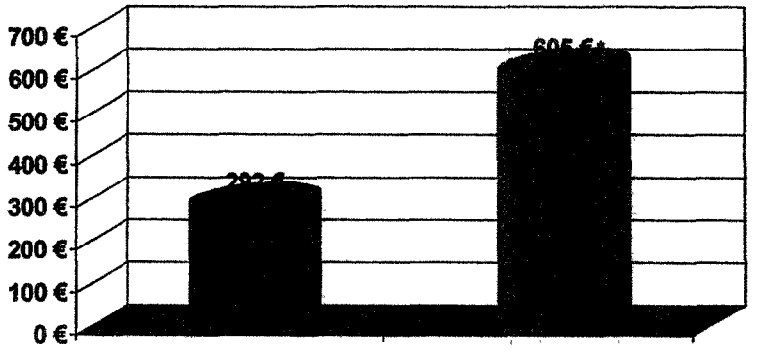
Pavelka et al, abstract submitted to ACR 2004

Why do the long-term therapeutic trials of CGS in knee OA, support the claim of disease prevention

- **Disease outcomes in longer-term follow-up**

3-year treatment with CGS prevented OA-related lower limb surgery, a clinically relevant disease outcome during an average further follow-up of 5 years. This may be due to the structure-modifying activity achieved during treatment and an overall delay in joint structure changes. In addition, patients previously on CGS may have a long-lasting symptomatic effect, a better quality of life and a lower utilisation of health resources.

Mean cost of health resources utilisation (in Euro) during the last year of the follow up.



p= 0.024
1 € = ~1.2 U.S.$

Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

Conclusions of the Follow-Up study

- During an average further follow-up of 5 years, previous 3-year treatment with glucosamine sulfate for prevention of knee OA clinically relevant outcomes:
  - Reduced the need for lower limb joint surgery

  In addition, the previous treatment:
  - Resulted in a significantly slower progression in joint structure changes
  - Induced a long-lasting symptomatic effect
  - Promoted a better quality of life

  and
  - a lower utilisation of health resources

Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

Mean (SD) SF-36 score at follow-up evaluation

All scores were higher in the former glucosamine sulfate group

Variables	Placebo N=43	Glucosamine Sulfate N=58	P
Physical function	52 (28)	56 (26)	0.45
Social function	66 (23)	76 (22)	0.04
Role physical	47 (36)	67 (36)	0.007
Role emotional	70 (37)	71 (39)	0.92
Mental health	54 (20)	59 (20)	0.18
Vitality	45 (18)	51 (16)	0.10
Pain	44 (26)	54 (24)	0.04
General health	49 (18)	57 (22)	0.05
Health change	45 (21)	49 (21)	0.39

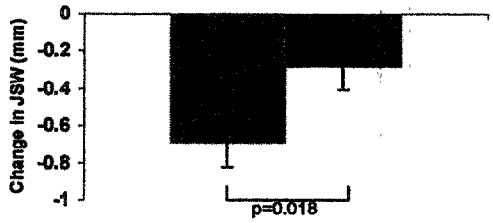
Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

Mean (SE) cost/use of health resources in the year prior to follow-up evaluation

Variables	Placebo N=43	Glucosamine Sulfate N=58
Cost of analgesics (€)	59 (23)	19 (3)
Cost of NSAIDs (€)	116 (31)	63 (17)
Total cost of OA drugs (€) (including analgesics, NSAIDs etc)	**204 (43)**	**108 (20)**
Number of visits to specialist	2.1 (0.5)	1.8 (0.3)
Number of paramedical visits for OA (physiotherapist, etc.)	17.4 (6.3)	6.6 (2.0)
Number of radiograps for OA	0.60 (0.14)	0.44 (0.09)
Number of gastroscopies	0.30 (0.07)	0.10 (0.04)
Number of non-OA exams	5.4 (1.6)	2.8 (0.6)

Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

Mean (SE) change in minimum JSW from trial enrolment to follow-up



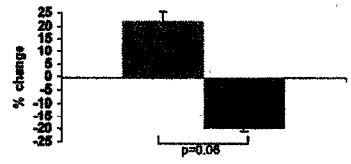
■Placebo ■Glucosamine Sulfate

Placebo N=35	Glucosamine Sulfate N=49	P
-0.69 (0.14)	-0.29 (0.12)	0.018

Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

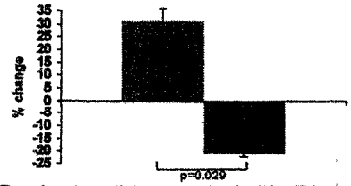
Mean (SE) WOMAC index % change from trial enrolment to follow-up

WOMAC total



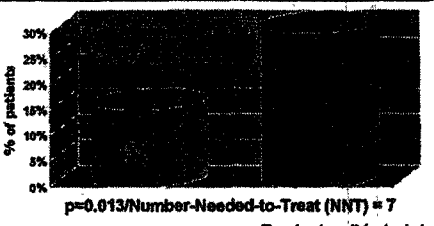
■Placebo (N=43) ■Glucosamine Sulfate (N=58)

WOMAC function



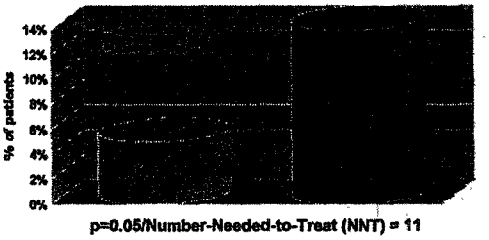
Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

Incidence of severe mean joint space narrowing (JSN>0.5 mm) after 3 years



p=0.013/Number-Needed-to-Treat (NNT) = 7

Reginster JY et al, Lancet. 2001; 357: 251-56



p=0.05/Number-Needed-to-Treat (NNT) = 11

Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23

Patients with >0.5 mm JSN during trial had a 3-fold risk increase for knee surgery during follow-up

Follow-up assessment	Follow-up patients with mean and/or minimum JSN >0.5 mm during trial		Relative Risk (95% CI) of knee surgery at follow-up if JSN>0.5 mm during trial
	Yes (n=54)	No (n=123)	
Number of patients with knee surgery	13	9	
Incidence of knee surgery	24.1% (13/54)	7.3% (9/123)	3.29 (1.50-7.23)

These data provide external validity to the trial arbitrary cut-off of 0.5 mm JSN to define severe joint structure damage.
Glucosamine sulfate had decreased by 50% (p=0.013) the incidence of JSN>0.5 mm during the trial.

Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

OA-related lower limb surgery during Follow-up

• NUMBER OF PATIENTS - Number of events	Placebo (N=86)	Glucosamine Sulfate (N=91)	Relative Risk (95% CI)	P
• Pts. with knee and/or hip surgery*	17	9	0.52 (0.23-1.06)	0.06
- Number of knee and/or hip surgeries	20	11	0.52 (0.26-1.02)	0.05
- Number of knee surgeries only	17	9	0.52 (0.23 to 1.06)	0.06

* Including knee or hip replacement, or joint debridement/meniscectomy

Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

OA-related lower limb surgery during Follow-up

• NUMBER OF PATIENTS - Number of events	Placebo (N=86)	Glucosamine Sulfate (N=91)	Relative Risk (95% CI)	P
• Pts. with knee and/or hip replacement	12	7	0.55 (0.23-1.33)	0.18
- Number of knee and/or hip replacements	15	9	0.56 (0.26-1.23)	0.14
- Number of knee replacements only	12	7	0.55 (0.23 to 1.33)	0.18

Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

Methods of the Follow-up study

- All 212 patients previously in the trial were invited, by phone or mail, to participate in a follow-up evaluation including a clinic visit or at least a telephone interview.
- All patients that could be contacted (N=177, i.e. 83% of the original sample, 86 formerly on placebo and 91 on CGS) were questioned about lower limb OA-related surgery occurring after the trial. Secondary outcomes could be assessed in a subset of 101 patients.
- The mean duration of follow-up after the study was 5 years (min. 3.8; max 8.0). Patients had received standard of care.

Reginster JY et al, Arthritis Rheum 2003, 48: 89 (ACR abstract)

Methods II of the Follow-up study

- 101 patients accepted a clinic visit and were also administered:
  - WOMAC questionnaire
  - SF-36 questionnaire
  - a questionnaire on the use of health resources during the previous year

  and, whenever possible, a knee radiograph was taken according to the conventional standing A-P technique used at the time of the trial, for the assessment of:
  - minimum JSN (medial tibiofemoral compartment)
- All follow-up analyses were performed in intention-to-treat, i.e. irrespectively of the duration of patient's involvement in the previous trial.

Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

Prevention of Osteoarthritis = Avoidance of Long-Term Disease Outcomes

- Osteoarthritis is a heterogenous condition in which symptoms do not readily correlate with joint structure changes.
- Although it can be diagnosed, staged and treated according to current guidelines, prevention of the disease may be referred to prevention of the clinically relevant outcomes, i.e. patient disability and/or the need for joint surgery.

Purpose of the Follow-Up study of the Reginster cohort

- To perform a follow-up evaluation in patients from the previous 3-year trial (Lancet 2001), to assess long-term disease outcomes including, as primary outcome:
  - The occurrence of osteoarthritis-related joint surgery

  and, as secondary outcomes:
  - Radiographic knee joint structure changes
  - Knee osteoarthritis symptoms
  - Quality of Life
  - Pharmacoeconomic impact on use of health resources

Reginster JY et al, Arthritis Rheum 2003, 48:89 (ACR abstract)

Why do the long-term therapeutic trials of CGS in knee OA, support the claim of disease prevention

- **Symptom- and Structure-Modifying effects in patients with milder characteristics at entry**

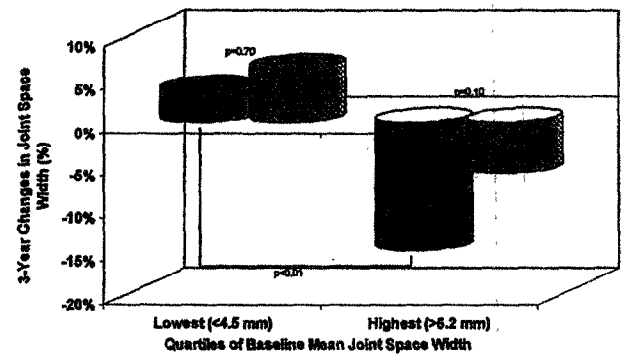
The structure-modifying effect of CGS was particularly evident in those patients with better preserved joint space at baseline, whose joint structure is closer to that of the general population. Conversely, CGS symptom-modifying effect is present irrespectively of baseline joint structure conditions, thus confirming both previous data on treatment (obtained in more severe patients) and the potential for prevention.

Why do the long-term therapeutic trials of CGS in knee OA, support the claim of disease prevention

- Mild to moderate characteristics of the patient population
- Data on the contralateral knee
- Symptom- and Structure-Modifying effects in patients with milder characteristics at entry
- **Disease outcomes in longer-term follow-up**
- Effects in prophylactic animal models
- Mechanism of action supporting short- and long-term effects on symptoms and prevention of joint structure changes

Correlation between baseline and 3-year changes in Joint Space Width (JSW)

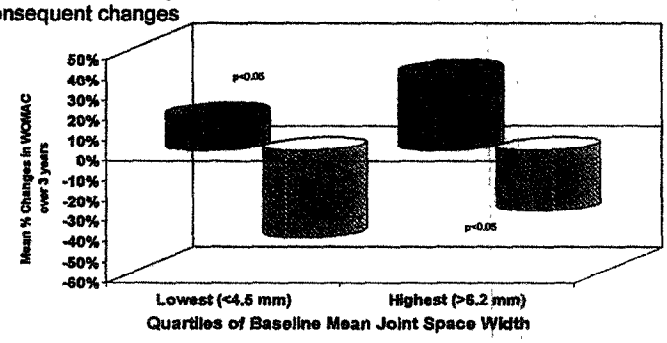
- A significant (negative) correlation was found with placebo (r=-0.34; p=0.003)
- The structure-modifying effect of GS was evident in disease progressors (those with more preserved JSW at baseline).



Bruyère et al, Osteoarthritis Cartilage 2003:11:1-5

Correlation between baseline joint structure and 3-year changes in symptoms

- Poor correlation between baseline or 3-year changes in joint space width and 3-year changes in symptoms, in the placebo group
- The symptom-modifying effect of GS occurred irrespectively of structural severity and consequent changes



Bruyère et al, 2002:Scand.J.Rheum.,31,13-6

Why do the long-term therapeutic trials of CGS in knee OA, support the claim of disease prevention

- **Data on the contralateral knee**

The contralateral knees of patients in the two long-term studies had baseline JSW values that are hard to differentiate from those of the general population. Nevertheless, the trend for the prevention of JSN was similar to that observed in the signal joint.

Why do the long-term therapeutic trials of CGS in knee OA, support the claim of disease prevention

- Mild to moderate characteristics of the patient population
- Data on the contralateral knee
- **Symptom- and Structure-Modifying effects in patients with milder characteristics at entry**
- Disease outcomes in longer-term follow-up
- Effects in prophylactic animal models
- Mechanism of action supporting short- and long-term effects on symptoms and prevention of joint structure changes

Enrolment Joint Space Width (JSW) and 3-year Joint Space Narrowing (JSN) in the contralateral knee

	Placebo (n=66)	Glucosamine sulfate (n=54)	Difference (95% CI)	P
Enrolment Mean JSW-mm, ave. (SD)	6.04 (1.13)	6.04 (1.22)	[redacted]	0.95
3-Years Mean JSN-mm, ave. (SD)	-0.54 (1.22)	-0.08 (1.09)	0.46 (0.04 to 0.88)	0.033

Reginster JY et al, Lancet. 2001; 357: 251-56

Enrolment Joint Space Width (JSW) and 3-year Joint Space Narrowing (JSN) in the contralateral knee

	Placebo (n=78)	Glucosamine sulfate (n=67)	Difference (95% CI)	P
Enrolment Minimum JSW-mm, ave. (SD)	4.72 (1.52)	4. 90 (1.39)	[redacted]	0.47
3-Years Minimum JSN-mm, ave. (95% CI)	-0.13 (-0.23 to –0.03)	-0.04 (-0.12 to 0.05)	-0.07 (-0.04 to 0.23	0.17

Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23

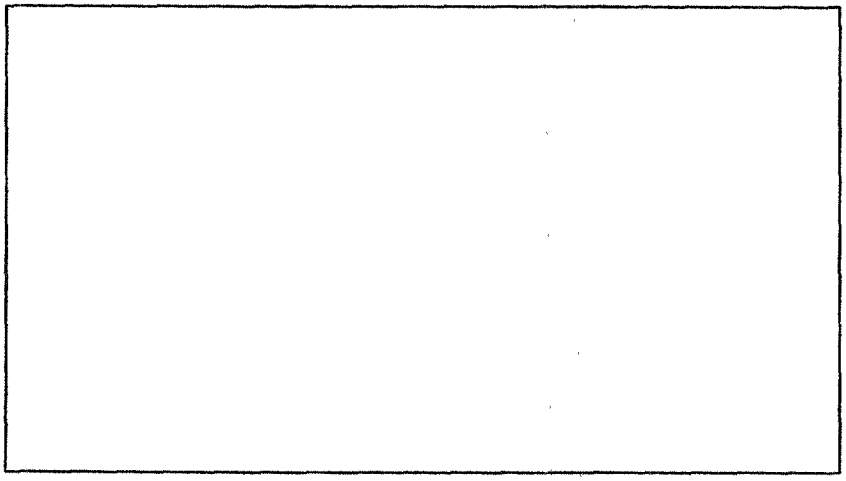
Why do the long-term therapeutic trials of CGS in knee OA, support the claim of disease prevention

- **Mild to moderate characteristics of the patient population**

Patients in the two long-term trials had mild to moderate symptoms at enrolment and, especially, they predominantly had mild joint structure changes. The effects observed in this population may therefore be transferred to the general population at risk for osteoarthritis.

Why do the long-term therapeutic trials of CGS in knee OA, support the claim of disease prevention

- Mild to moderate characteristics of the patient population
- **Data on the contralateral knee**
- Symptom- and Structure-Modifying effects in patients with milder characteristics at entry
- Disease outcomes in longer-term follow-up
- Effects in prophylactic animal models
- Mechanism of action supporting short- and long-term effects on symptoms and prevention of joint structure changes



Baseline knee OA characteristics for joint structure and symptoms

	Placebo (N=106,101)	Glucosamine Sulfate (N=106,101)	P
Joint Structure			
01 Study			
Mean joint space width-mm	5.39 (1.29)	5.23 (1.36)	0.38
Minimum joint space width-mm	3.96 (1.24)	3.82 (1.32)	0.49
02 Study			
Minimum joint space width-mm	3.63 (1.57)	3.69 (1.48)	0.24
Symptoms			
01 Study			
Total WOMAC index-VAS	940 (485)	1030 (474)	0.17
02 Study			
Total WOMAC index-points	30.5 (14.4)	30.7 (14.4)	
Lequesne index-points	8.9 (2.3)	8.9 (2.3)	0.91

Data are average (SD)

** 01-Reginster JY et al, Lancet. 2001; 357: 251-56*

***02- Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23*

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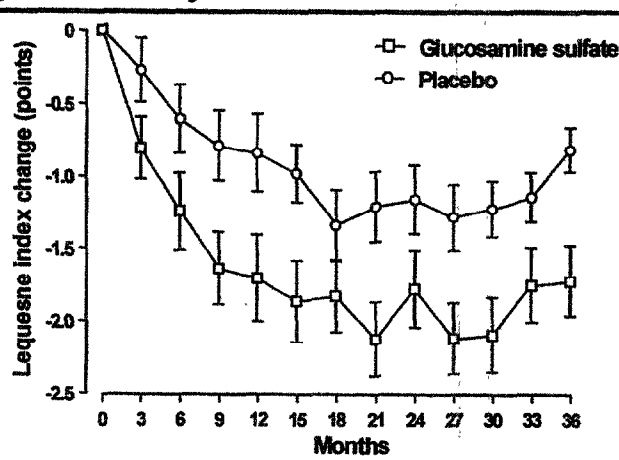
Intent-to-treat change in symptom scores (in points: average and 95% CI) after 3 years compared to baseline

	Placebo (N=101)	Glucosamine sulfate (N=101)	Difference	p
Lequesne index	-0.82 (-1.1 to -0.51)	-1.7 (-2.2 to -1.2)	0.91 (0.34 to 1.5)	.002
WOMAC total	-4.9 (-6.5 to -3.2)	-8.0 (-9.8 to -6.3)	3.1 (0.77 to 5.5)	.010
WOMAC pain	-1.3 (-1.7 to 0.88)	-2.0 (-2.4 to -1.5)	0.7 (0.06 to 1.3)	.029
WOMAC function	-3.7 (-4.9 to -2.5)	-5.8 (-7.1 to -4.4)	2.1 (0.28 to 3.9)	.024
WOMAC stiffness	0.11 (-0.12 to 0.34)	-0.31 (-0.55 to 0.07)	0.42 (0.09 to 0.75)	.012

Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23

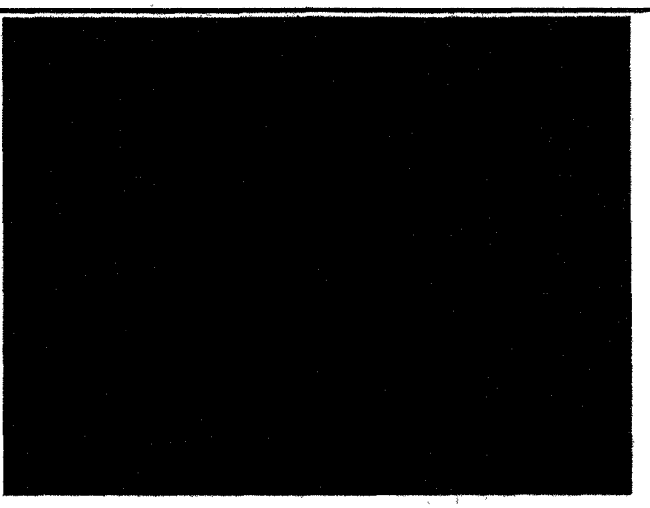
Intent-to-treat Lequesne index change at clinic visits throughout the study



P=0.004 between groups on ANOVA for repeated measures

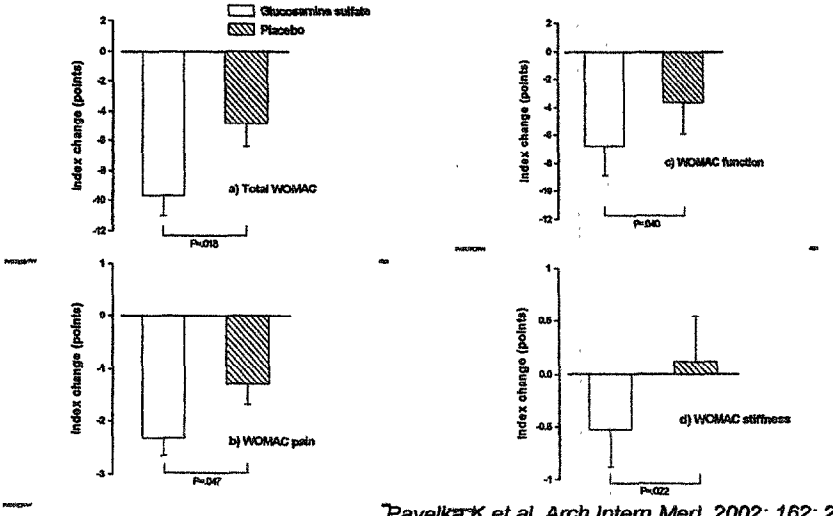
Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23

Change in the WOMAC subscales after 3 years (ITT-sum of VAS scores)



Reginster JY et al, Lancet. 2001; 357: 251-56

Change in total WOMAC index and pain, function and stiffness subscales after 3 years (PP-sum of Likert scale scores)



Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23

Total WOMAC % change (average and 95% CI) after 3 years in evaluable patients (per-protocol)

	Placebo (N=71)	Glucosamine sulfate (N=68)	Difference (95% CI)	p
Total WOMAC % change	9.8% (-14.6 to 34.3%)	-24.3% (-37.0 to –11.6%)	34.1% (6.4 to 61.8%)	0.016

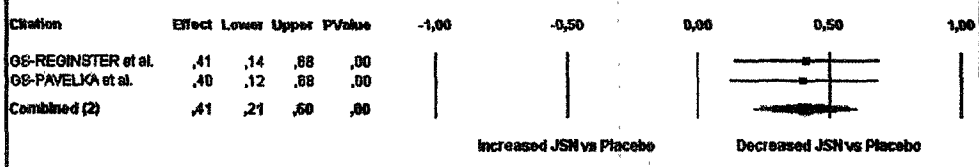
Reginster JY et al, Lancet. 2001; 357: 251-56

Total WOMAC % change (average and 95% CI) after 3 years in the intention-to-treat (worst case scenario) analysis

	Placebo (N=106)	Glucosamine sulfate (N=106)	Difference (95% CI)	p
Total WOMAC % change	9.8% (-6.2 to 25.8%)	-11.7% (-20.3 to –3.2%)	21.6% (3.5 to 39.6%)	0.020

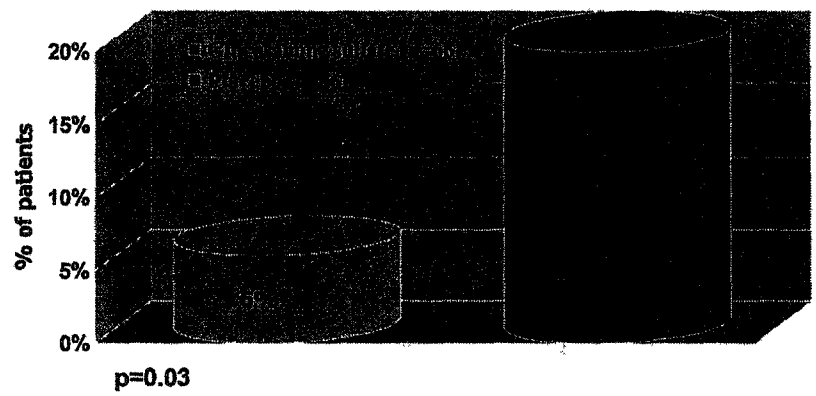
Reginster JY et al, Lancet. 2001; 357: 251-56

Prevention of joint structure impairment by glucosamine sulfate 1500 mg/day at three years in the two long-term studies: effect size vs. placebo



Richy F et al.
Structural and Symptomatic Efficacy of Glucosamine and Chondroitin Sulfate in Knee Osteoarthritis: A Comprehensive Meta-Analysis.
Arch Intern Med 2003; 163: 1514-22

Secondary radiographic features of OA: Proportion of patients worsening their Atlas osteophyte score at the end-point



p=0.03

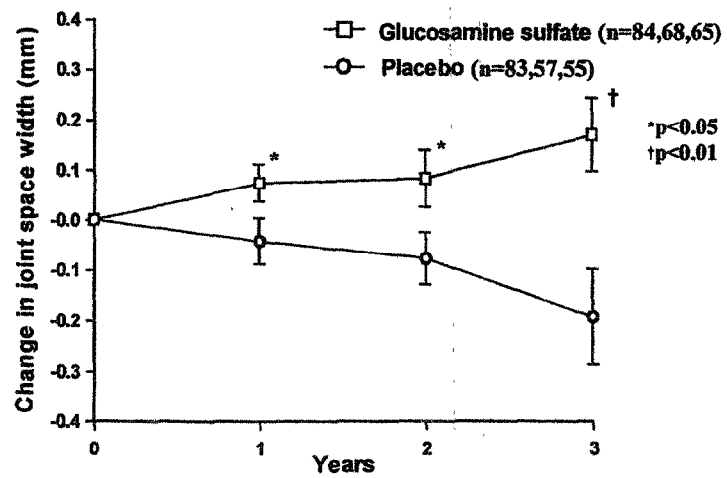
Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23

Joint Space Narrowing (in mm: average and 95% CI) at each year of treatment in the intention-to-treat (worst case scenario) analysis

Year	Placebo (N=101)	Glucosamine sulfate (N=101)	Difference between treatments	p
1	-0.04 (-0.12 to 0.03)	0.05 (-0.007 to 0.12)	0.097 (0.0006 to 0.19)	.049
2	-0.08 (-0.14 to –0.02)	0.03 (-0.05 to 0.11)	0.11 (0.01 to 0.20)	.027
3	-0.19 (-0.29 to –0.09)	0.04 (-0.06 to 0.14)	0.23 (0.09 to 0.37)	.001

Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23

Joint Space Narrowing (mean and sem) in patients completing each year of the study



Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23

Primary outcome measures

- ***Symptom Modification:***
  - WOMAC index (a validated composite index of pain, stiffness and physical function for knee OA); VAS version (01 Study*) and LK version (02 Study **) (total score, i.e. sum of the 24 component item scores, and pain, function and stiffness subscales).
  - LEQUESNE index (a validated composite index of pain, movement limitation and walking capacity for knee OA) (02 Study**).

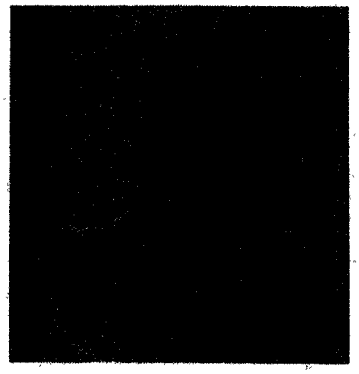
** 01-Reginster JY et al, Lancet. 2001; 357: 251-56*

***02- Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23*

Joint Space Narrowing (average and 95% CI) after 3 years in the intention-to-treat (worst case scenario) analysis

	Placebo (N=106)	Glucosamine sulfate (N=106)	Difference between treatments	p
Mean joint space narrowing (mm)	-0.31 (-0.48 to –0.13)	-0.06 (-0.22 to 0.09)	0.24 (0.01 to 0.48)	0.043
Minimum joint space narrowing (mm)	-0.40 (-0.56 to –0.24)	-0.07 (-0.22 to 0.07)	0.33 (0.12 to 0.54)	0.003

Reginster JY et al, Lancet. 2001; 357: 251-56



Joint degeneration/cartilage deterioration as modifiable risk factors/surrogate endpoints for OA risk reduction

- Joint degeneration is an indicator/predictor of OA, as it is fundamental for OA diagnosis and it is invariably present in all patients with definite OA.
- Cartilage deterioration is the most widely accepted surrogate of joint degeneration. It can be indirectly assessed by plain radiography, measuring changes in joint space width (JSW).
- JSW is accepted by all scientific and regulatory guidelines (FDA and EMEA) to assess progression of OA, as it is:
  - *Valid*:
    Accurate measure of cartilage thickness in cadaver studies
  - *Reliable*:
    Good precision over repeated measurements
  - *Sensitive*:
    Epidemiological studies have shown a loss of ~0.1 mm/year in knee OA

New long-term clinical studies of Glucosamine Sulfate for disease modification in osteoarthritis

Study design

- Prospective, randomised, placebo-controlled, double-blind, parallel-group trials of 3-year duration.

Patient selection

- 212 (01 Study*) and 202 (02 Study**) patients of both genders aged over 45 yrs with primary knee OA (ACR criteria).

Treatments

- Crystalline Glucosamine Sulfate 1500 mg once-a-day continuously for 3 years, or placebo.

Results

- Glucosamine Sulfate is the first clinically tested agent able to prevent the progression of OA joint structure deterioration (as determined by radiographic joint space narrowing), functional impairment and pain (by the validated algo-functional indexes of Lequesne and WOMAC).

** 01 - Reginster JY et al, Lancet 2001; 357: 251-56*

***02 - Pavelka K et al, Arch.Int.Med 2002; 162: 2113-2123*

Primary outcome measures

- ***Structure Modification:***

  Weight-bearing (standing), antero-posterior radiographs of each knee,at enrolment and for 3 years by a standardised technique (patient positioning and radiographic procedure, including fluoroscopy). Minimum joint space width of the medial compartment of the tibio-femoral joint assessed by visual reading with the aid of a 10x magnifying lens graduated in 0.1 mm intervals (on the signal joint, i.e. the narrowest side at enrolment).

  Mean joint space width was also assessed in the 01 Study* by digital image analysis.

  Secondary radiographic features of OA (osteophytes) were assessed in the 02 Study** by Atlas scoring.

** 01-Reginster JY et al, Lancet. 2001; 357: 251-56*

***02- Pavelka K et al, Arch Intern Med. 2002; 162: 2113-23*

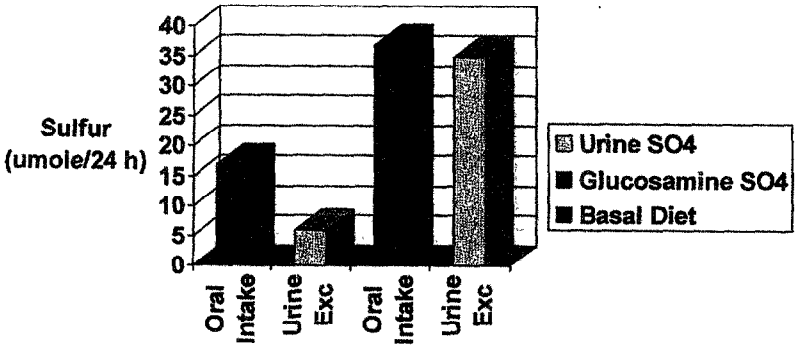
Systematic Reviews and Meta-Analyses of RCTs

- Towheed et al, Cochrane Library 2001; issue 2
  - Placebo or active comparator-controlled trials (mean duration 6.25 weeks)
  - 16 trials reviewed (12 considered), 2029 patients (all but one with CGS)
  - Quality scores "collectively as good, if not better, than NSAID trials in OA", even improving with more recent trials
  - Large effect sizes on OA symptoms and good safety
  - The only trial with glucosamine HCl gave less favourable results. Authors concluded that presence of sulfates and especially the formulation (all glucosamine sulfate trials performed with the Rotta preparation) seems to be important.

Systematic Reviews and Meta-Analyses of RCTs

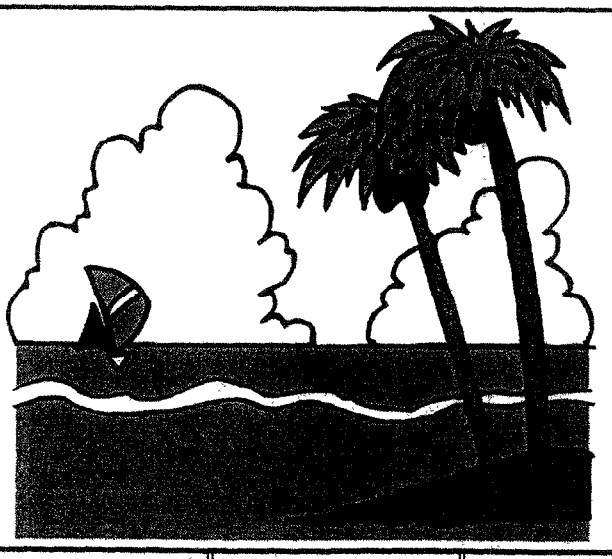
- Richy et al, Arch Intern Med 2003;163:1541-22
  - Placebo-controlled trials of glucosamine sulfate perfomed according to current standards. Included the two long-term studies of CGS
  - 7 trials reviewed (5 with CGS)
  - High quality scores: 90% in average
  - Moderate effect sizes on OA symptoms, calculated with a more conservative approach than in the two previous meta-analyses. The two studies with other formulations of GS emerged as those with the lowest effect size.
  - Consistent effect on prevention of joint structure damage progression in the two long-term trials of CGS
  - Good safety even in the long-term
  - Exclusion of publication bias

Oral intake of SO4 on urine excretion

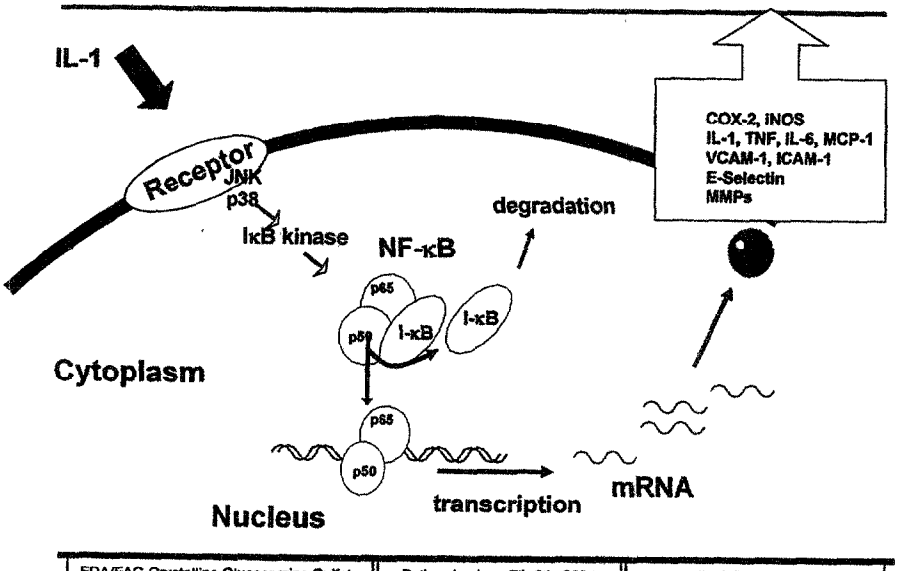


Cordoba & Nimni, OAC 2003;11:228

UCLA

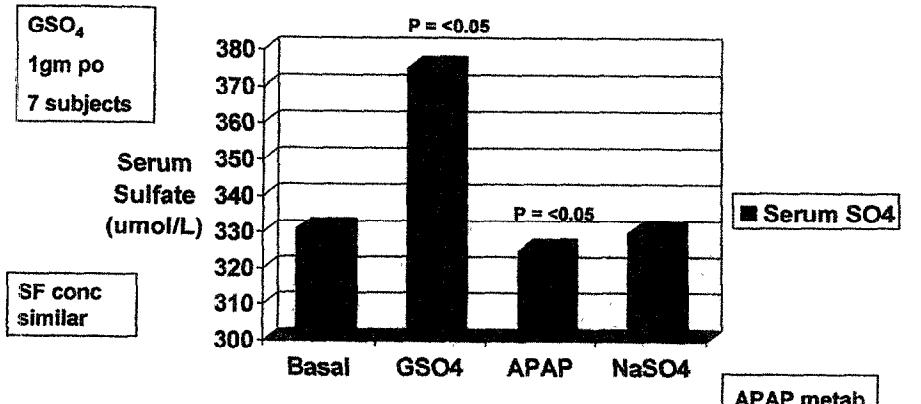


NF-κB regulation



Sulfate on serum SO_4 levels

GSO_4
1gm po
7 subjects

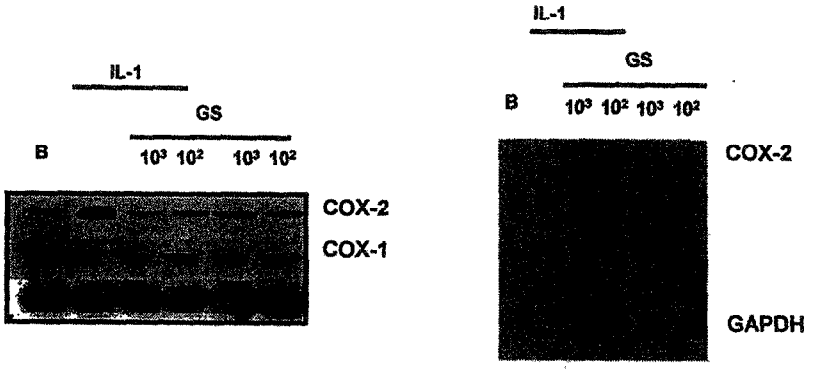


SF conc similar

APAP metab By sulfation

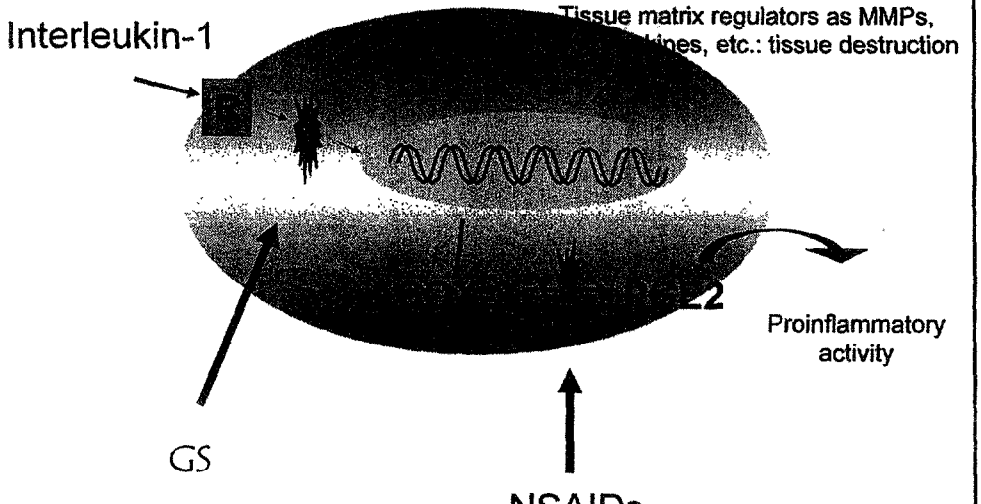
Hoffer, Metabolism 2001;50:767

GS inhibits COX-2 mRNA expression and protein synthesis in OA chondrocytes stimulated with IL-1β

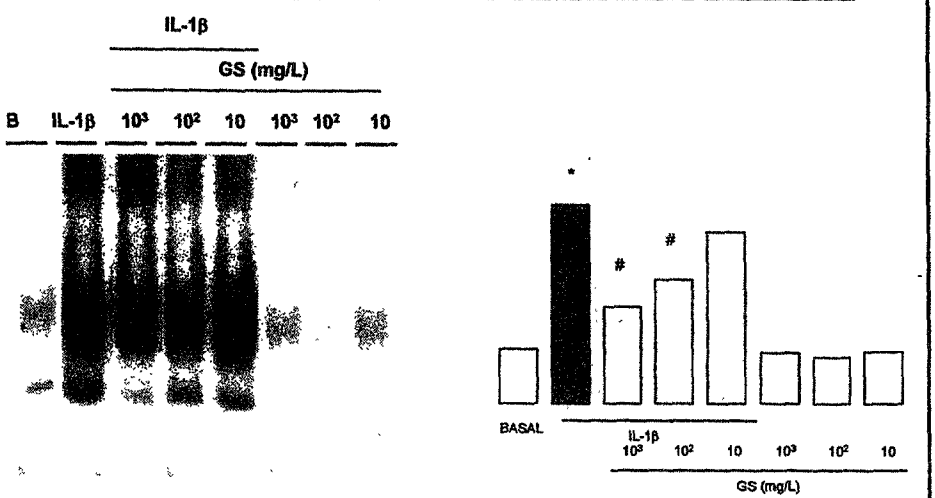


Largo et al, Osteoarthritis Cartilage 2003, 11: 290-8

Cellular response & the action of GS

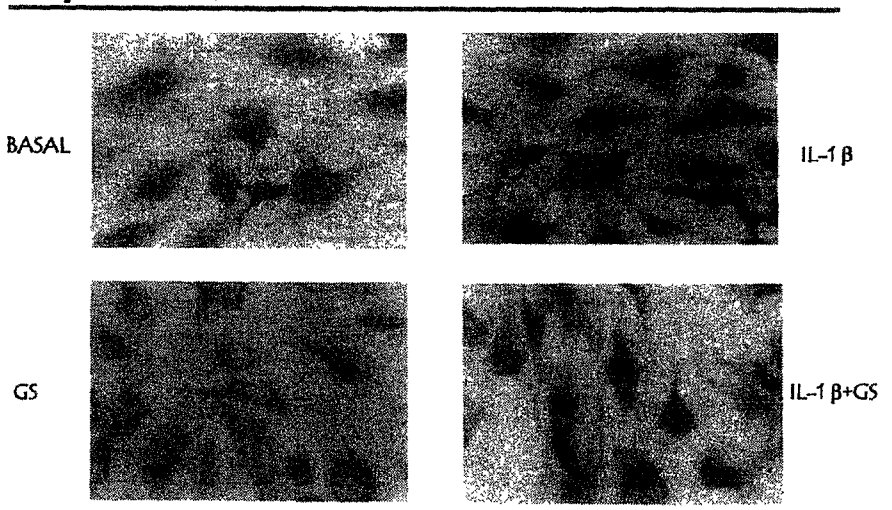


Inhibition of NF-kB activity by glucosamine sulfate



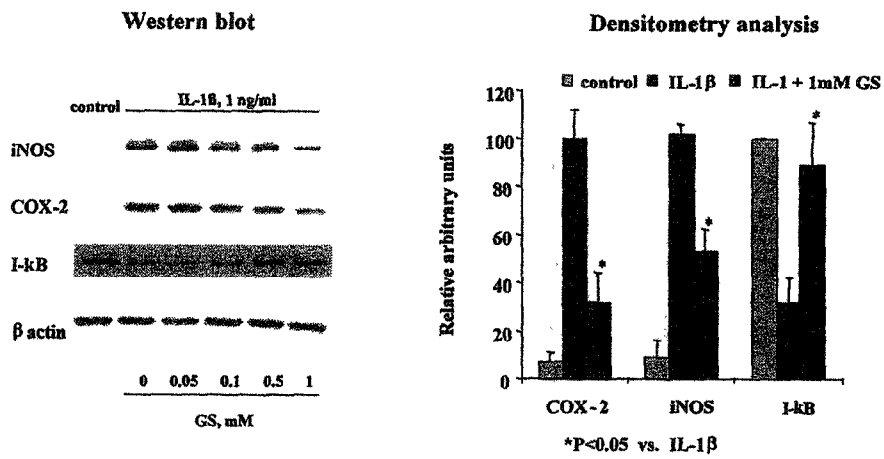
Largo et al, Osteoarthritis Cartilage 2003, 11: 290-8

GS inhibits nuclear translocation of p50 NF-kB subunit



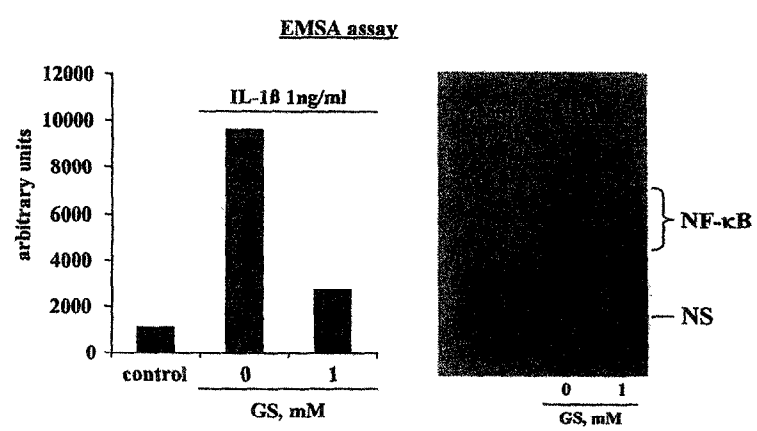
Largo et al, Osteoarthritis Cartilage 2003, 11: 290-8

GS reverses IL-1-induced COX-2 and iNOS increased expression and I-kB decreased expression in chondrocytes



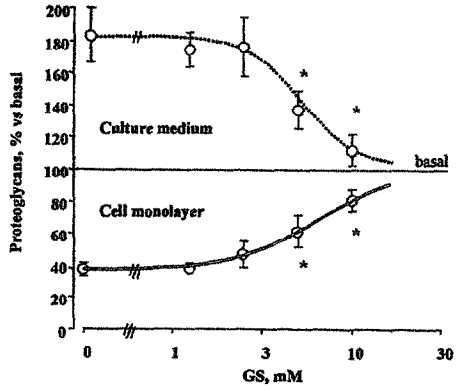
Letari et al, Arthritis Rheumatism 2003, 48:S286

GS reduces IL-1-induced NF-kB activation assessed by nuclear translocation



Letari et al, Arthritis Rheumatism 2003, 48:S286

GS inhibits matrix degradation stimulated by IL-1 in chondrocyte cultures

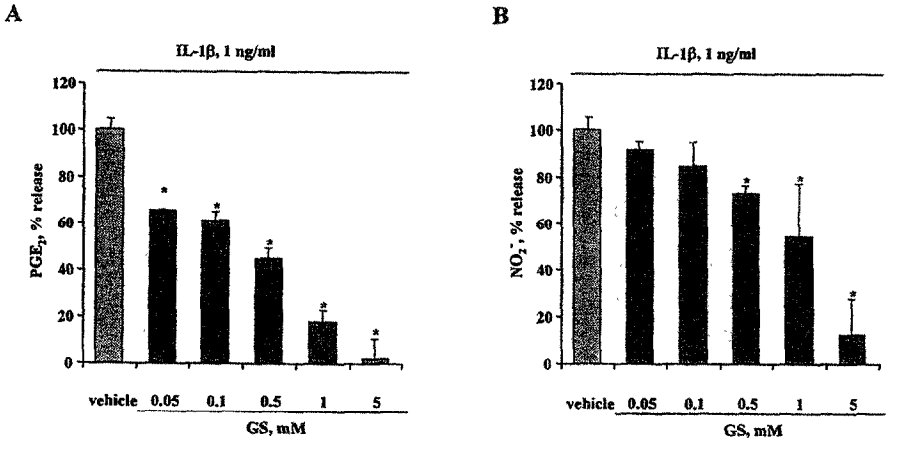


The content in GAG and proteoglycans in untreated cells was used as basal control

*p<0.05 vs. IL-1ß only (1 ng/ml)

Letari et al, Arthritis Rheumatism 2003, 48:S286

GS inhibits IL-1 induced PGE_2 and NO release from chondrocytes



*p<0.05 vs. IL-1β + vehicle

Letari et al, Arthritis Rheumatism 2003, 48:S286

In vitro studies with Glucosamine Sulfate (GS) in human osteoarthritic chondrocytes

Anticatabolic Effects

- GS decreases stromelysin
  - *Dodge GR et al. Osteoarthritis Cartilage 2003;11: 424-32*
- Glucosamine decreases aggrecanase
  - *Sandy et al. Biochem J, 1998; 335: 59-66*
- GS decreases PLA2 activity
- GS decreases collagenase activity
  - *Piperno et al. Osteoarthritis and Cartilage, 2000; 8: 207-12*

Antiinflammatory effects of Glucosamine Sulfate

Glucosamine sulfate

- does not inhibit cycloxygenase activity
- Inhibits moderately the release of proteolytic enzymes
- Inhibits lysosomal enzymes
- Inhibits the generation of aggressive superoxide radicals
  - *Setnikar et al. Arzneimittelforschung, 1991; 41, 157-161*
- Inhibits the synthesis of inducible nitric oxide
  - *Shikhman et al. J Immunol, 2001; 166: 5155-60*

Glucosamine Sulfate

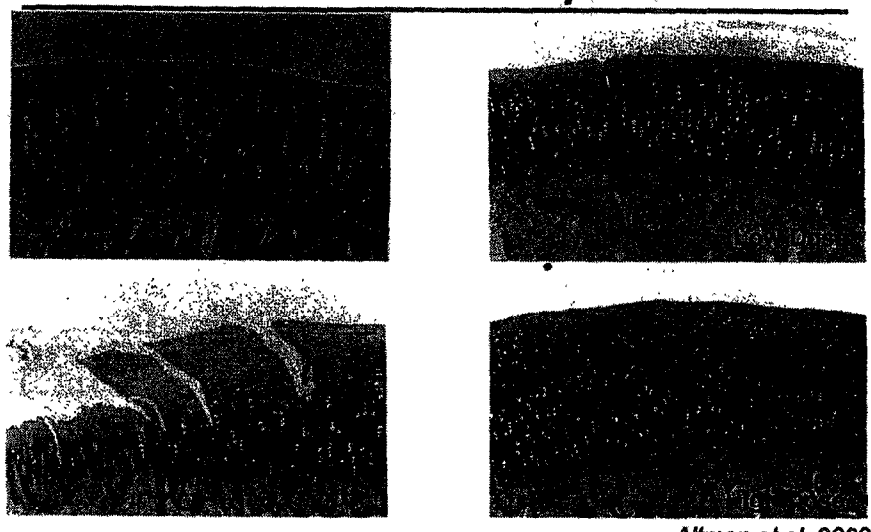
Mechanism of Action

In vitro studies with Glucosamine Sulfate (GS) in human osteoarthritic chondrocytes

Anabolic Effects

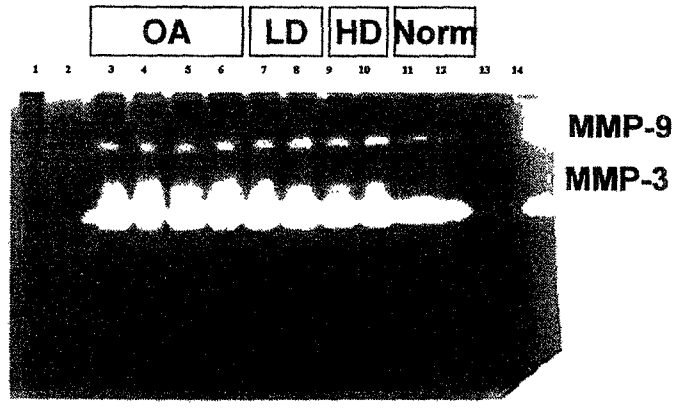
- GS increases proteoglycan synthesis
  - *Bassleer et al. Osteoarthritis Cartilage, 1998; 6 : 427-34*
  - *Pipemo et al. Osteoarthritis Cartilage, 2000; 8: 207-12*
- GS increases perlecan and aggrecan mRNA
  - *Dodge GR et al. Osteoarthritis Cartilage 2003;11: 424-32*
- GS increases PKC production
- GS increases adhesion of chondrocytes to fibronectin
  - *Pipemo et al. Osteoarthritis Cartilage, 1998; 6: 393-99*

Glucosamine Sulfate in Lapine OA



Altman et al, 2002

Glucosamine Sulfate in Lapine OA

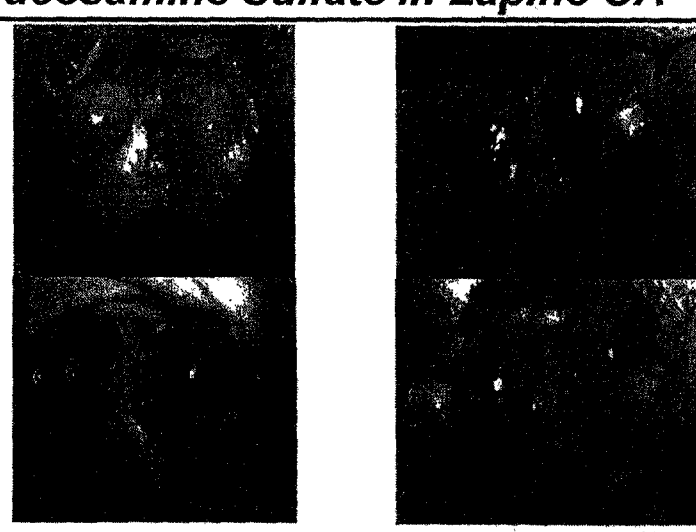


Transferrin

Crystalline glucosamine sulfate in Lapine OA

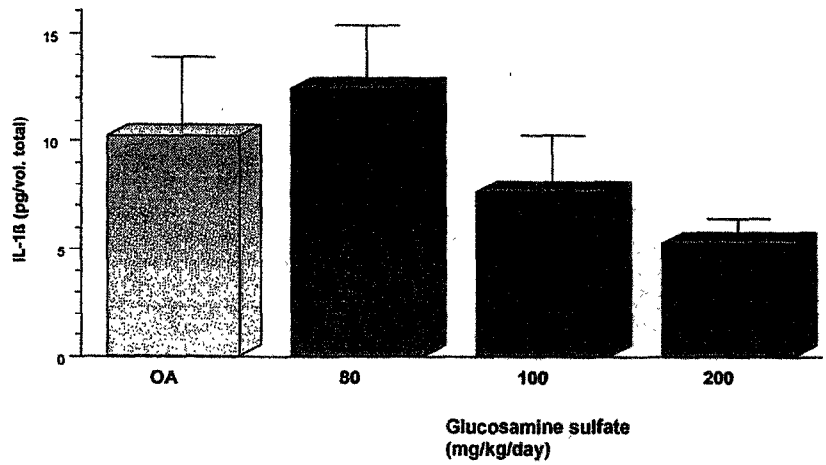
Group	Glucosamine	Surgery
Normal	Placebo	No
Low Dose	100mg/kg/d	Yes
High Dose	200mg/kg/d	Yes
OA	Placebo	Yes

Glucosamine Sulfate in Lapine OA



Altman et al, 2002

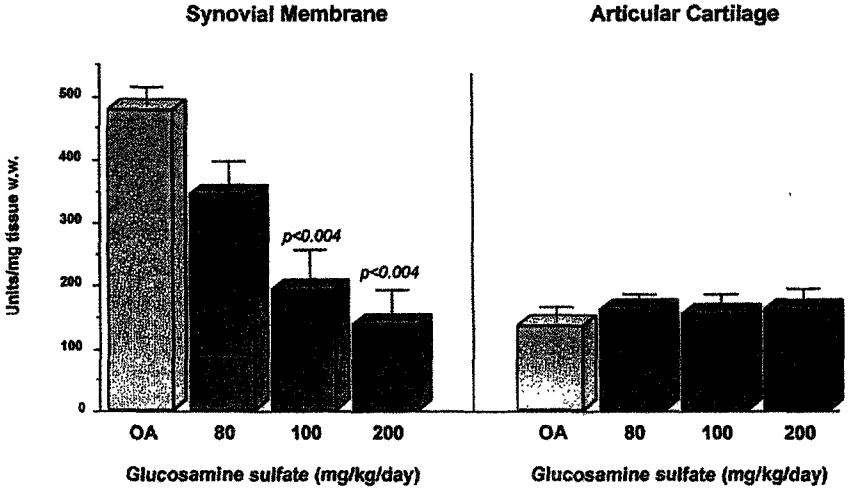
Synovial fluid IL- 1β



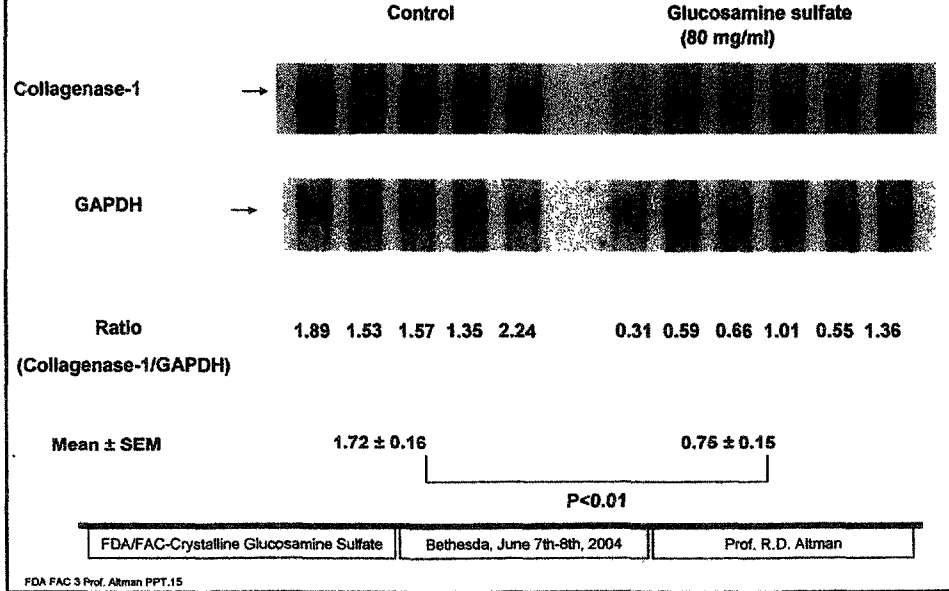
Glucosamine Sulfate in biomechanical and OA models

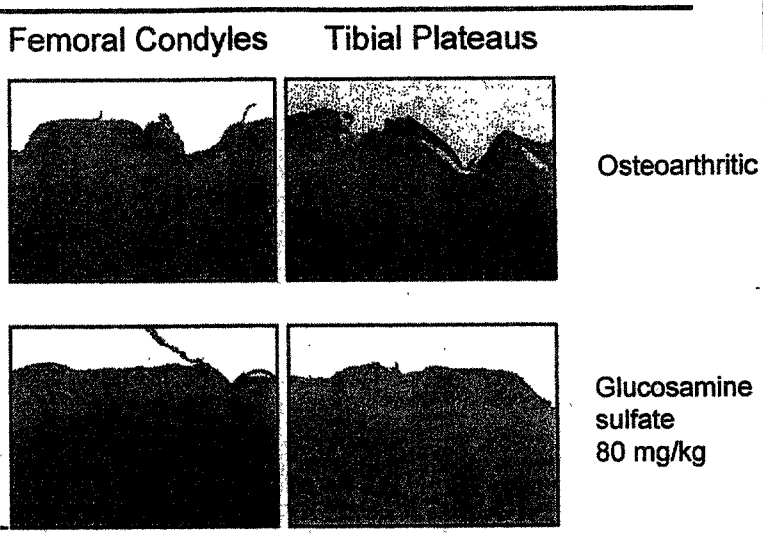
- GS reverses the decrease in proteoglycan synthesis and aggrecan mRNA expression linked to static compression
  - *Gouze 2001*
- GS reverses the increase in MMP-3 mRNA expression caused by loading
  - *Gouze 2001*
- GS minimizes the degree of damage on mechanically traumatized cartilage explants
  - *Krueger 2001*
- GS significantly reduces cartilage destruction in rabbit OA induced by anterior cruciate ligament transection (ACL)
  - *Conrozier 1998*
- GS increases proteoglycan content of repairing young rabbit cartilage
  - *Oegema 2001*
- GS reduces metalloprotease expression and the joint structural changes in dog OA induced by ACL sectioning
  - Pelletier 2002
- **GS reduces metalloprotease expression and the joint structural changes in rabbit OA induced by hemimeniscetomy**
  - *Altman 2002*

Stromelysin activity



Osteoarthritic



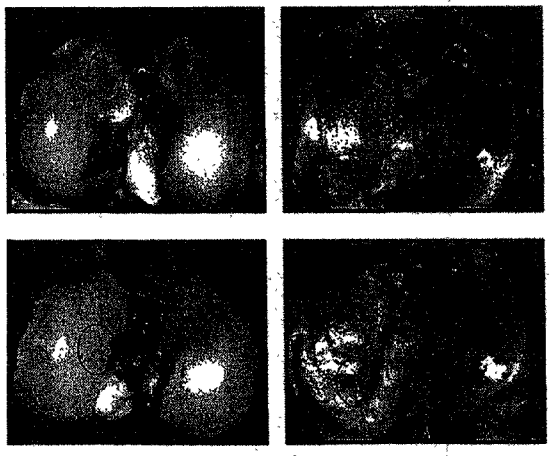


Macroscopic and microscopic grading of femoral condyles cartilage lesions

	Osteoarthritic	Glucosamine sulfate 80 mg/kg
Macro lesion size (mm^2)	19.0±3.8	11.9±4.0
Histological grade (0-6)	2.92±0.37	1.58±0.34*

*$p<0.02$ vs. osteoarthritic

Femoral Condyles Tibial Plateaus



Osteoarthritic

Glucosamine sulfate 80 mg/kg

Experimental protocol

- Operated group
  - Anterior cruciate ligament sectioning
- Operated and treated group
  - Anterior cruciate ligament sectioning
  - Glucosamine sulfate
    - 80 mg/kg/day/po
    - 100 mg/kg/day/po
    - 200 mg/kg/day/po

✓ Dogs were sacrificed and tissues examined 8 weeks after surgery. Glucosamine sulfate was given orally for 8 weeks beginning immediately after surgery.

Glucosamine Sulfate in biomechanical and OA models

- GS reverses the decrease in proteoglycan synthesis and aggrecan mRNA expression linked to static compression
  - *Gouze 2001*
- GS reverses the increase in MMP-3 mRNA expression caused by loading
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  - *Oegema 2001*
- **GS reduces metalloprotease expression and the joint structural changes in dog OA induced by ACL sectioning**
  - ***Pelletier 2002***
- GS reduces metalloprotease expression and the joint structural changes in rabbit OA induced by hemimeniscetomy
  - *Altman 2002*

Effect of Crystalline Glucosamine Sulfate on the prevention of canine experimental osteoarthritic lesions, metalloprotease activity and IL-1ß production

J-P Pelletier, DV Jovanovic, J Fernandes, J Martel-Pelletier

Osteoarthritis Research Unit

Centre hospitalier de l'Université de Montréal

Hôpital Notre-Dame

Montréal, Québec, Canada

Glucosamine Sulfate

Prophylactic Administration of
Glucosamine Sulfate
in Animal Models of OA

Glucosamine sulfate in biomechanical and OA models

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  - *Altman 2002*

June 7th-8th

FDA

Food Advisory Committee Meeting

Crystalline Glucosamine Sulfate

Crystalline Glucosamine Sulfate: Further Considerations on Clinical Studies, Quality, Pharmacokinetics, Pharmacology, Significant Scientific Agreement and Safety

ROTTA Pharmaceuticals Inc.

Why "glucosamine" formulations other than CGS do not have the same body of evidence to support any claim

Forms of glucosamine other than the original crystalline glucosamine sulfate, non-exhaustively including:

- glucosamine hydrochloride
- N-acetyl-glucosamine
- other "glucosamine sulfate" formulations,

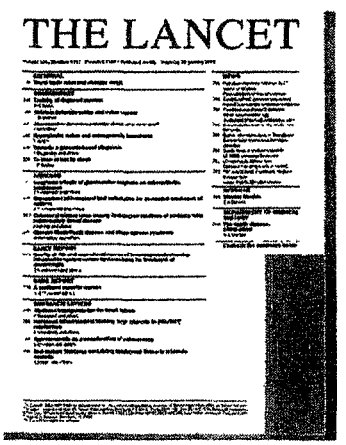
or combinations of these substances with other ingredients, e.g.

- Glucosamine/chondroitin sulfate combinations,

may not share the same pharmacological, clinical, quality, or pharmacokinetic properties of the original substance.

1st 3 Year Study published in The Lancet

- Excerpts from the Lancet - Jan 27, 2001 Vol 357


THE LANCET

- "*Treatment assignment*

  Crystalline glucosamine Sulphate (Dona, Viatril-S or Xicil, Rotta Research Group, Monza Italy) is a defined pure substance that is symthesised from chitin, and in which glucosamine, sulphate, chloride, and sodium icons are present in stoichiometric ratios of 2:1:2:2"
- "This product has been approved at this once daily dosage as a prescription treatment for osteoarthritis in many countries in Europe and elsewhere"
- "In this study, glucosamine sulfate was approved as a prescription drug, therefore, our results cannot be generalized to other glucosamine products (or compound mixtures) such as those available in some countries as dietary supplements"

Safety of Glucosamine Sulfate - The insulin resistance issue

- Animal studies with suprapharmacological I.V. doses of glucosamine suggested an interaction with the hexosamine pathway and an increase in insulin resistance.
- At least 4 studies and the trial experience with CGS suggest that this mechanism is not operative in humans:
  - Monauni et al, Diabetes 2000
    i.v. glucosamine 1.6-5.0 µmol/kg.min for 4 h in 10 healthy volunteers did not affect insulin levels or secretion during IVGTT or euglycemic insulin clamp, but only slightly increased plasma fasting glucose levels.
  - Pouwels et al, J Clin Endocrinol Metab 2001
    Intra-arterial CGS 4 µmol/dL.min for up to 5 h in 18 healthy volunteers had no effect on insulin-induced glucose uptake and thus insulin sensitivity.

Safety of Glucosamine Sulfate - The insulin resistance issue II

- *Scroggie et al, Arch Intern Med 2003*
  A 1500 mg glucosamine HCl/1200 mg chondroitin combination given for 3 months to 26 type 2 diabetes patients vs. 12 on placebo, did not modify hemoglobin A_{1c} concentrations, or diabetes management.
- *Tannis et al, Osteoarthritis Cartilage 2004*
  1500 mg/day glucosamine sulfate for 3 months to 19 healthy volunteers did not alter serum insulin or plasma glucose during OGTT; there were no significant changes in glycated hemoglobin levels.

- *Rovati et al, Lancet 1999*
  Fasting plasma glucose did not change in short-term trials of CGS in OA, even in patients with baseline hyperglycaemia and tended to decrease in the 3-year study of Reginster et al.
- *Pavelka et al, Arch Intern Med 2002*
  Four patients developed diabetes during the 3-year treatment: 1 on CGS and 3 on placebo.

The ACR practice guidelines on knee and hip OA

- The latest version of the American College of Rheumatology (ACR) guidelines (a consensus document instead of an evidence-based recommendation) were published in September 2000 and could not take into account the two long-term trials of CGS, or the Cochrane and Richy meta-analyses, and could not make therefore any specific recommendations on glucosamine sulfate *[Altman RD, Hochberg MC, Moskowitz RW, Schnitzer, TJ (ACR subcommittee). Recommendations for the medical management of OA of the hip and knee. Arthritis Rheum 2000]*
- "The documented efficacy of glucosamine...., requires us to reassess the use of glucosamine as a first line agent at least for patients with knee OA who have mild to moderate disease". *Hochberg MC. What a difference a year makes: reflections on the ACR recommendations for the medical management of OA. Curr Rheumatol Rep 2001.*

Safety of Glucosamine Sulfate

- All systematic reviews and meta-analyses support the safety of glucosamine sulfate in humans.
- The short-term trials of CGS report an incidence of patients with AEs between 6% and 15%, with drop-outs for AEs in <4% There are no significant differences with placebo, but a significant advantage over conventional NSAIDs.
- In the two long-term trials, the safety of CGS was similar to that of placebo.
- Being regulated as a prescription drug in over 40 countries of the world, regular Periodic Safety Update Reports (PSURs) are generated at ICH standards. Information from these PSURs indicates that out of estimated 30,400,000 patient/months receiving the substance, there were only 209 spontaneous adverse reaction reports, with no safety signals.

The EULAR practice guidelines on knee OA

- In the recent EULAR practice guidelines, glucosamine sulfate was scored the highest Level of Evidence (1A) and the highest Strength of Recommendation (A). Out of 34 pharmacological and non pharmacological modalities, this was attributed only to 6 of them.
- In addition, glucosamine sulfate was attributed the highest median quality score for the trials performed (24 out of maximum 28), and among the highest effect sizes vs. placebo.

The EULAR practice guidelines on knee OA

Examples among modalities with evidence/recommendation 1A/A or at least 1B/A.

Modality	Level of evidence	Strength of recomm	Quality score*	Effect size**
Glucosamine sulfate	1A	A	24	0.43-1.02
Conventional NSAIDs	1A	A	17	0.47-0.96
Coxibs	1B	A	23	0.50
Acetaminophen	1B	A	20	-
Education	1A	A	13	0.28-0.35
Exercise	1B	A	15	0.57-1.0

* Median ** Range , if available

Significant scientific agreement (SSA) on the use of Glucosamine Sulfate for OA

- SSA is reflected in the most recent practice guidelines issued by the top rheumatology scientific organisations.
- The only practice guideline that takes into account most of the new evidences on glucosamine sulfate is the evidence-based document from the European League Against Rheumatism (EULAR), that was published in November 2003. (KM Jordan et al, Ann Rheum Dis 2003;62:1145-55)

EULAR Recommendations 2003: An evidence based medicine approach to the management of knee osteoarthritis Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT).

KM Jordan, NK Arden, M Doherty*, B Bannwarth, J Bijlsma, P Dieppe, K Gunther, H Hauselmann, G Herrero-Beaumont, P Kaklamanis, S Lohmander, B Leeb, M Lesquesne, B Mazieres, E Mola, K Pavelka, A Pendleton, L Punzi, U Serni, B Swoboda, G Verbruggen, I Zimmerman-Gorska, M Dougados*.
*Co-Chairs of Task Force

Ann Rheum Dis 2003; 62: 1145-55

Why "Glucosamine" formulations other than CGS do not have the same body of evidence to support any claim

Conclusions

- Forms of glucosamine other than the original CGS formulation may not share the same quality, pharmacological, pharmacokinetic or, especially, clinical properties of the original substance.
- Besides not supporting any claim for other glucosamine formulations, care should be used when extrapolating results of clinical trials with these other formulations to the original CGS preparation, unless a clear pharmacokinetic/clinical equivalence is shown.

Why "Glucosamine" formulations other than CGS do not have the same body of evidence to support any claim

"In contrast to earlier industry-funded trials for knee OA, recent studies have generated negative results. While there will be a tendency to assume that these studies were negative because of the absence of any conflict of interest, a number of issues must be taken into consideration. These include design issues and important differences in sample characteristics. Ultimately, it is clear that more work needs to be done to clarify issues surrounding the efficacy and utility of various glucosamine compounds".

McAlindon T, Rheum Dis Clin N Am 2003;29:789-801
"Why are clinical trials of glucosamine no longer uniformly positive?"

Glucosamine PK parameters after oral CGS (750, 1500, or 3000 mg once-daily)

Parameter	750 mg	1500 mg	3000 mg
T_{max} [h][1)]	3 (0.5-6)	3 (1.5-4)	4 (3-4)
$C_{ss,max}$ [ng/ml][2)]	1069.2±675.30	1601.9±424.85	2503.1±1835.3
AUC_{ss} [ng.h/ml][2)]	9696.67±4214.75	14563.7±4138.16	22094.6±6984.08*
AUC_t [ng.h/ml][2)]	14323.0±5582.4	20216.4±5021.27	27990.5±8034.69*

1) Median and range
2) Mean±SD
* $p<0.05$ vs. 750 mg when dose-normalised

Persiani et al, abstract submitted to ACR 2004

Oral bioavailability and dose-proportionality of CGS in man

- **Summary**:
  - Glucosamine is rapidly bioavailable after oral administration and is distributed to extravascular compartments.
  - Pharmacokinetics are linear up to 1500 mg once-daily, but deviates from dose-proportionality at higher doses.
  - The elimination half-life (t½) is 15 h and supports once daily dosing.
  - Steady-state maximal concentrations are in the range effective in inhibiting IL-1 intracellular signalling pathway, that mediate the substance preventive/treatment effects.

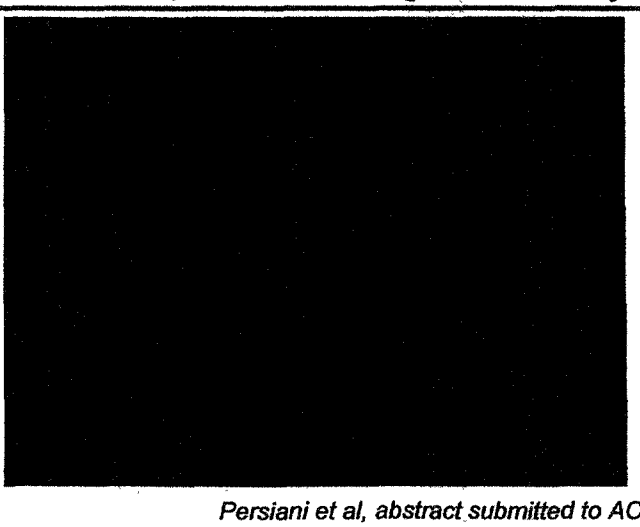
Persiani et al, abstract submitted to ACR 2004

Oral bioavailability and dose-proportionality of CGS in man

- **Methods**: 12 healthy volunteers (6M, 6F) received 3 consecutive once-daily oral administrations of the CGS soluble powder formulation 750, or 1500, or 3000 mg, in a randomised, cross-over fashion.
- **Results**: Endogenous glucosamine was detected in plasma (10.4-204 ng/ml, with low intra-subject variability) and basal levels were therefore subtracted. The pharmacokinetic properties at steady state could be described.

Persiani et al, abstract submitted to ACR 2004

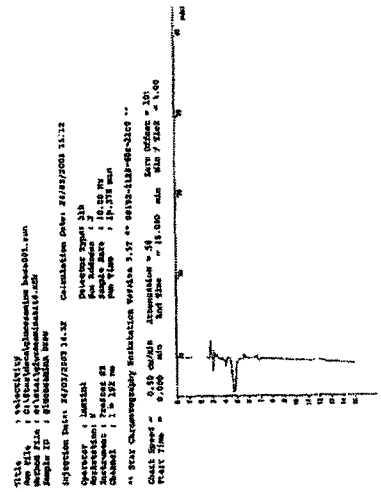
Mean glucosamine plasma concentration vs time profiles after repeated doses of 750, 1500 and 3000 mg CGS once daily



Persiani et al, abstract submitted to ACR 2004

HPLC Method for Glucosamine (USP / NF 2004)

Chromatogram of Glucosamine free base solution



Why "glucosamine" formulations other than CGS do not have the same body of evidence to support any claim

Pharmacokinetic considerations

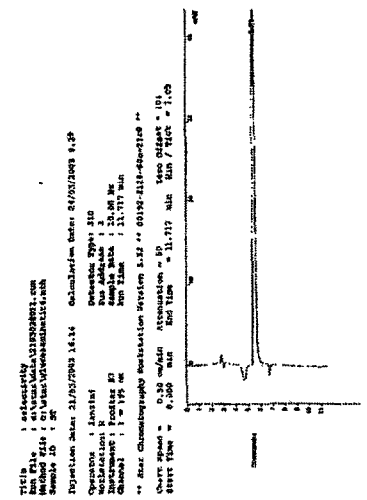
- The knowledge about glucosamine pharmacokinetics has been limited by the poor sensitivity and specificity of the available cold, chemical methods. Slightly better information could be obtained using [^{14}C] uniformly labelled glucosamine, with all consequent limitations of this approach.
  The information available for CGS has been recently reviewed (Setnikar and Rovati, 2001) and supported the original substance for which, in any case, an exhaustive clinical trial package is available. Nevertheless, it helped low quality products, preventing them from showing bioequivalence with the original CGS.
- Very recently, a Liquid Chromatography with Mass Spectrometry detection (LC-MS/MS) method was validated for the determination of glucosamine in plasma (LoQ:6.25 ng/ml) and allowed to study the oral bioavailability and dose-proportionality of the original formulation in man (Persiani et al, abstract submitted to ACR 2004).

DONA™ Caplets/Packets Analytical Methods

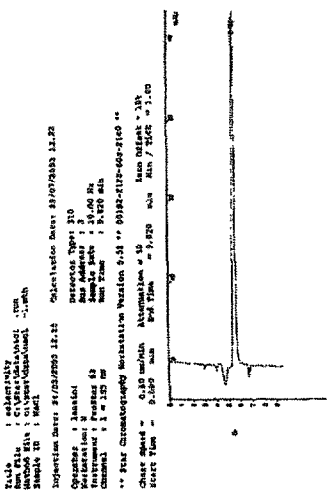
- The amount of Glucosamine Sulfate contained in DONA is detected by potentiometric methods.
- The methods proposed are validated for specificity, linearity, accuracy and precision.
- Differently from other originators of dietary supplements containing glucosamine, Rottapharm does not use the high-performance liquid chromatography method described in the USP/ NF 2004.
- The USP/NF 2004 method does not detect "glucosamine" but only the chloride ions present in Glucosamine Hydrochloride or in Glucosamine Sulfate Sodium Chloride.

HPLC Method for Glucosamine (USP / NF 2004)

Chromatogram of Glucosamine Hydrochloride solution



Chromatogram of NaCl solution



Weak rationale for glucosamine/chondroitin sulfate combinations

- Chondroitin sulfate is a glycosaminoglycan normally present in the cartilage matrix and consisting of a high M.W., long chain of repeating units of sulfated residues of glucuronic acid and N-acetyl-galactosamine (N-ac-gal), obtained with extraction processes from animal tissues (mostly of bovine origin, in the USA).
- Oral absorption of high molecular mass polymers is questionable. PK studies (Conte et al, 1995) have shown that the largest plasma peak consists of one of the constituents monomers, N-ac-gal.
- Very early studies had shown that N-ac-gal might induce metabolic activities similar to that of its precursor glucosamine, although with a lower potency (Karzel and Domenejoz, 1971)
- It may be speculated therefore that the clinical activity reported for chondroitin sulfate in some trials may be similar to that of low dose glucosamine sulfate. Adding chondroitin to a glucosamine HCl preparation may only slightly increase the dose of glucosamine and provide sulfates, thus explaining the effects shown in few trials on OA symptoms, but it is not known how these would compare with full dose CGS alone.

Why "glucosamine" formulations other than CGS do not have the same body of evidence to support any claim

Quality considerations

- The Rotta CGS formulation is regulated as a prescription drug in Europe and elsewhere and is thus subject to strict quality controls.
- In a recent investigation, Russel et al (J. Rheumatol 2002;29:2407-9) found that out of 14 nutritional supplement formulations of "glucosamine sulfate" commercially available in North America, only 2 contained over 80% of the labelled glucosamine content. For 12 formulations, the % of the stated amount ranged between 41 and 66% only.
- This observation follows a previous one from the University of Maryland (Adebowale et al, JANA 2000;3:37-44) in which, in 14 products with glucosamine HCl or sulfate, deviations from label claims ranged from 25% to 115%

Why "glucosamine" formulations other than CGS do not have the same body of evidence to support any claim

Clinical considerations – Glucosamine trials

- 86% of trials included in the available meta-analyses and the two high quality long-term trials have been performed with Rotta CGS.
- The few and small clinical trials conducted on other sources of glucosamine, besides having several methodological limitations in many instances, yielded less consistent, or even unfavourable results than those with CGS:
  - Houpt et al, J Rheumatol 1999
    8-week RCT of glucosamine HCl
    Not significant improvement vs placebo
  - Rindone et al, West J Med 2000
    8-week RCT of a "glucosamine"
    No difference vs. placebo in severe knee OA patients
  - Hughes and Carr, Rheumatology 2002
    6-month RCT of potassium chloride glucosamine sulfate
    No difference vs placebo in a "pragmatic" trial on all grades of knee OA severity, with background NSAIDs.

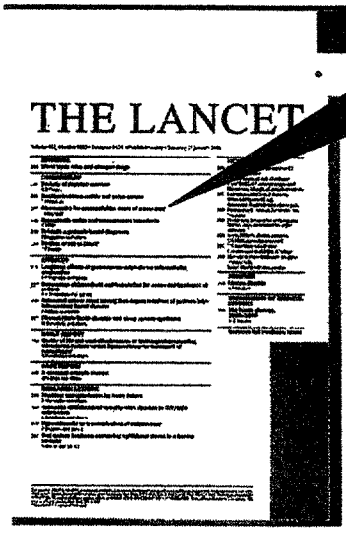
Why "glucosamine" formulations other than CGS do not have the same body of evidence to support any claim

Clinical considerations – Glucosamine/chondroitin trials

- Very few and small studies of glucosamine/chondroitin combinations have inconclusively suggested its efficacy on the short-term control of OA symptoms:
  - Leffler et al, Mil Med 1999
    16-week benefit vs placebo
  - Das and Hammad, Osteoarthritis Cartilage 2000
    6-month benefit vs placebo
- Due to the lack of a comparator arm with the original CGS, it is unknown whether the effects observed are of lower, similar, or higher magnitude than with the standard substance alone.
- A synergistic effect has never been shown in any clinical trial.

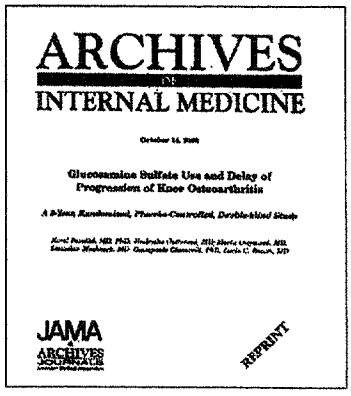
Commentary in The Lancet *for the 1st 3 Year Study*

Tim McAlindon – Arthritis Center, Boston University Medical Center


THE LANCET

- By [redacted] Commentary in the Lancet
  - [redacted] 3-year randomised placebo-controlled trial suggest that an oral agent, glucosamine sulphate, retards the progression of symptomatic knee osteoarthritis. The study is a landmark in OA research, not only for its scientific results, but also for highlighting vexing issues in this area."
  - "Certainly, the study by Jean Yves Reginster and colleagues shows many hallmarks of a well-conducted trial…"
  - "Since glucosamine is generally self-prescribed, the likely primary beneficiary of this trial will be the nutritional-product industry rather then the pharmaceutical company that sponsored the trial, even though the results may not be generalisable to the highly variable formulations of nutritional products"

2nd and Confirmatory 3 Year Study published in Archives of Internal Medicine


ARCHIVES
OF
INTERNAL MEDICINE

October 14, 2002

Glucosamine Sulfate Use and Delay of Progression of Knee Osteoarthritis

A 3-Year, Randomized, Placebo-Controlled, Double-Blind Study

JAMA
ARCHIVES JOURNALS

REPRINT

- Excerpts from Archives of Internal Medicine
  - "In this trial, we use Crystalline Glucosamine Sulfate, that is, the original Glucosamine Sulfate described in most of the literature and available as prescription drug for osteoarthritis in several European countries and other countries and as a nutritional supplement in the US (Dona, Viatril-S, or Xicil; Rotta Pharmaceuticals Inc., Wall, NJ)"
  - "Glucosamine derivatives are popular dietary supplements in the United States and other countries, exploiting the opportunity provided by the American Dietary Supplement Health and Education Act and the clinical research data obtained with glucosamine sulfate approved as a prescription drug for the treatment of osteoarthritis in Europe and elsewhere. The latter was used in our study and in most of the previous clinical experiences; at present, it is difficult to generalize these results to the highly variable and uncontrolled formulations of the other nutritional products claiming a glucosamine content"